Armed Forces College of Medicine

AFCM

Neurotropic vitamins (B1 & B12)

By

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Lecture key points

1. The active forms and functions of B1 & 12 vitamins
2. Vitamins (B1& B12) deficiencies & their clinical disorders

INTENDED LEARNING OBJECTIVES (ILO)

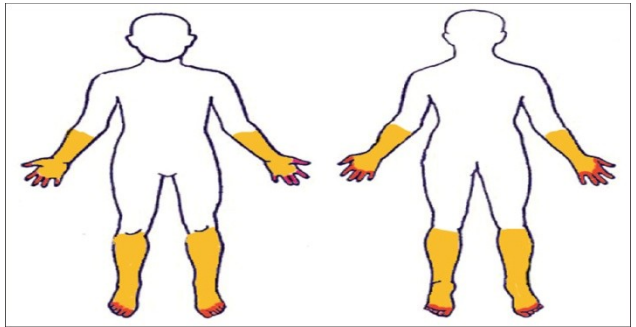
By the end of this lecture the student will be able to:

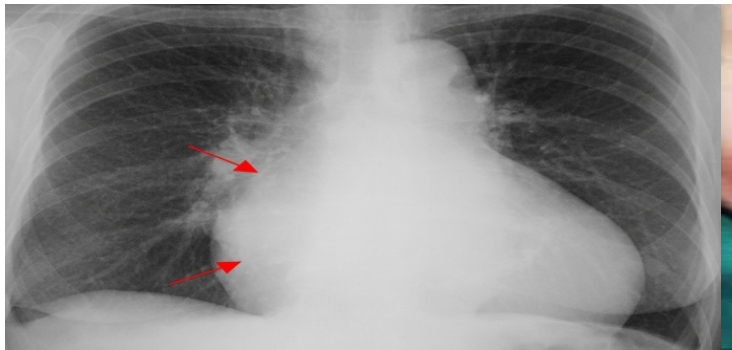
1. **Distinguish the active forms and functions of vitamins (B1 & 12)**
2. **Correlate vitamins (B1& B12) deficiencies to their clinical disorders**

Case scenario

22 years old woman was brought to the emergency unit complaining of res tory distress , vomiting , and weakness. mination revealed mus and numbn on also de and enlargement. Lab revealed decreased urinary thiamine level.

1. Enumerate symptoms & signs?
2. what is the probable diagnosis?
3. what are the function of thiamine (vitamin B1)?
4. Explain the biochemical basis of symptoms





Neurotropic vitamins

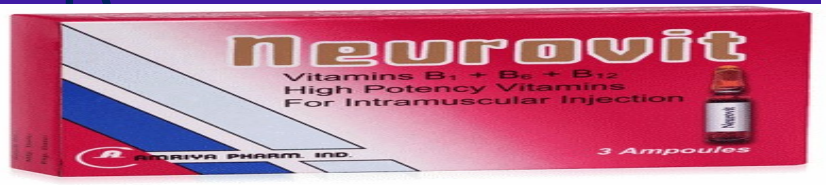
Vitamin B complex

- **Thiamine (B1)**
- **Riboflavin (B2)**
- **Nicotinic acid (B3)**
- **Pantothenic acid (B5)**
- **Pyridoxine (B6)**
- **Biotin**
- **Folic acid (B9)**
- **Cobalamins (B12)**

"**Neurotropic**" B **vitamins** : are especially important for the healthy nervous system "**neurotropic**".

This group of **vitamins** is composed of :

- Thiamine (B1)
- Niacin (B3)
- Pyridoxine (B6)
- Cyanocobalamin (B12) .
- Healthy CNS also need vitamin E



Food sources of vitamin B complex

All

1. Animal Sources:

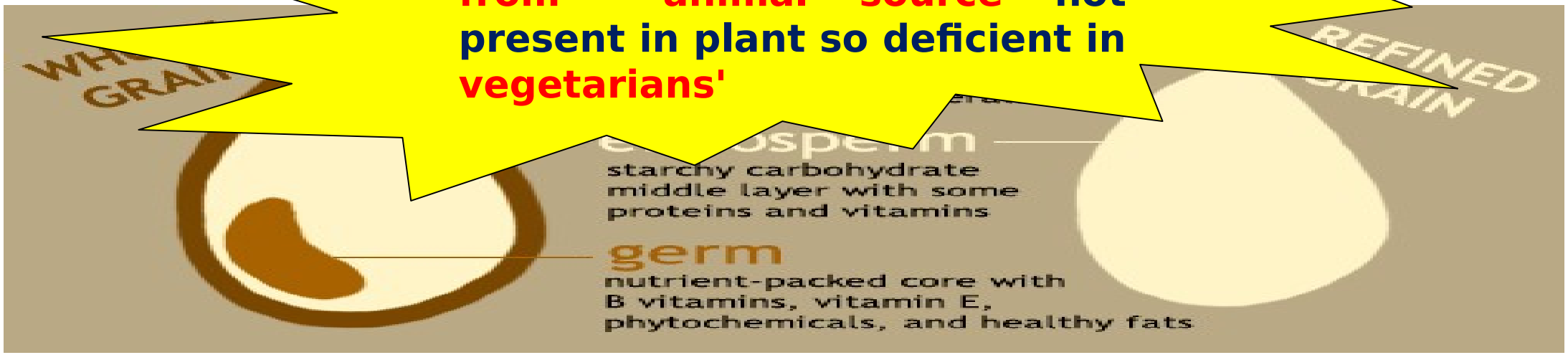
- Heart, liver, kidneys, meats, fishes, eggs and milk
- Intestinal bacteria form most members of the vitamin B complex

2. Plant Sources:

Green leafy vegetables, legumes, fruits, cere[illegible] and yeast are good plant sources.

البلدى بالرده والشوفان .

Vitamin B12 supplied only from animal source not present in plant so deficient in vegetarians'



Vitamin B l (Thiamine or Anti-Beri Beri)

Active form : thiamine pyrophosphate (TPP).

Functions of TPP: act as coenzymes for

1-Acts as coenzyme for oxidative decarboxylation of α-keto acids:

e.g.:

- **Pyruvate dehydrogenase complex**

  (pyruvate to → acetyl-CoA)

- **α-Ketogluterate dehydrogenase complex**

  (α-ketoglutarate to → succinyl-CoA)

http://image.wikifoundry.com/image/3/1FmGWC-VTPlGAxL1fVrvsg40870/

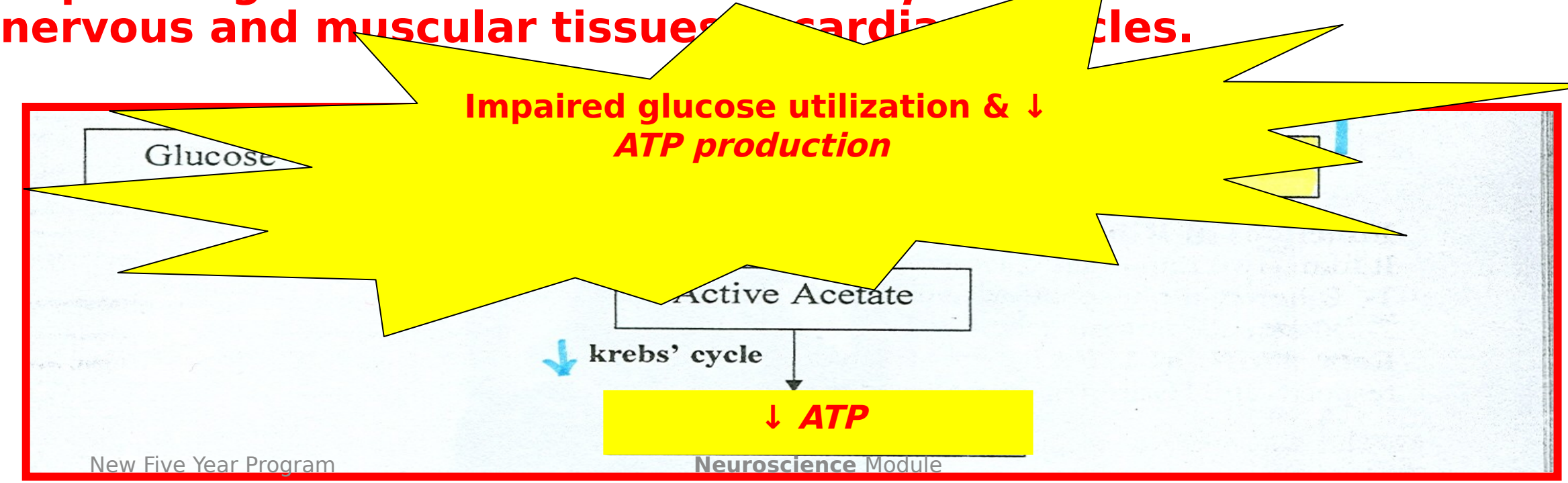
Vitamin B1 deficiency

Biochemical basis of clinical manifestations

-Pyruvate oxidation is impaired and pyruvate is converted to → lactate resulting in ↑ *blood* level of *pyruvate and lactate*.

-Also, Krebs cycle is affected due to ↓ activity of α-ketoglutrate (α-KG) dehydrogenase.

Impaired glucose utilization & ↓ *ATP production* will affect mainly nervous and muscular tissues, cardiac muscles.



Clinical manifestations (Beri-Beri)

1-Early stage :Dry Beri Beri

- **Neurological Manifestation:**
  ***Peripheral neuritis (Stock and gloves)*, mental confusion and muscular weakness.**
- **GIT Manifestations:**
  Anorexia, nausea and vomiting.

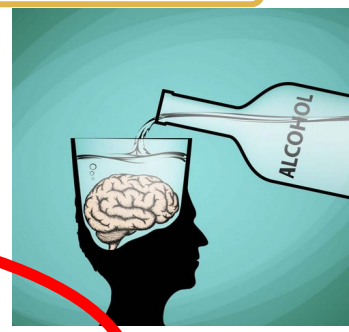
2-Late stage : Wet Beri Beri

- Cardio-Vascular Manifestations:

Cardiac enlargement, weakness and may be heart failure.

Edema (wet beri-beri).

Wernicke-Korsakoff syndrome



Causes

- Thiamine deficiency primarily in association with chronic alcoholism due to dietary insufficiency
- Or impaired intestinal absorption of the vitamin.

Characterized by:

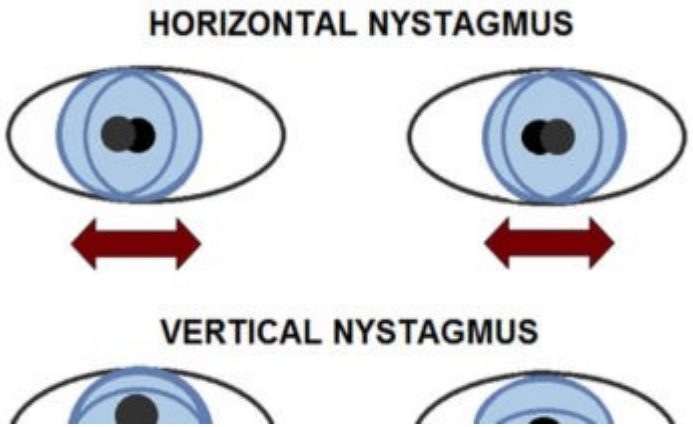
- Confusion
- Ataxia,
- Rhythmic to-and-fro motion of the eyeballs (nystagmus)
- Memory problems
- Hallucinations

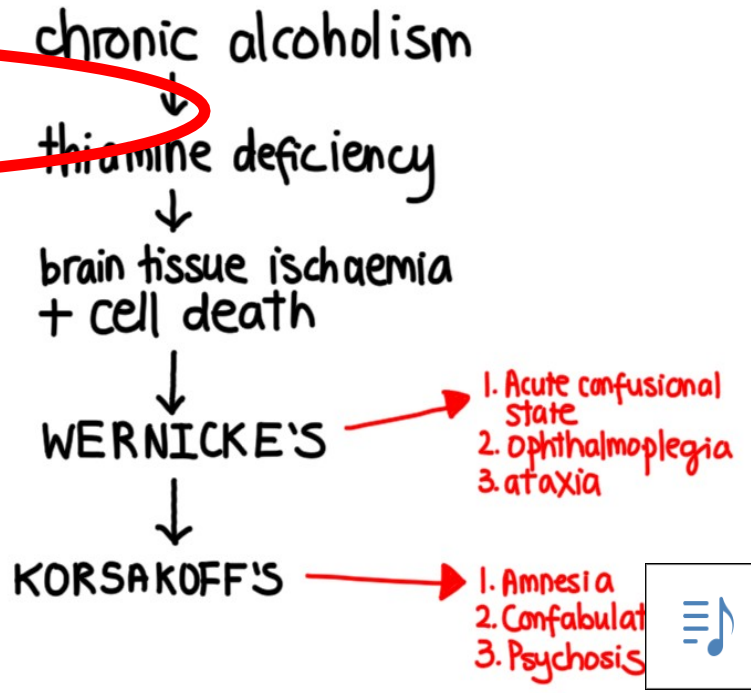
Wernicke encephalopathy (Acute reversible stage)

Korsakoff dementia (chronic irreversible stage)

Treatment:

- Thiamine supplementation.
- Recovery of memory is incomple





Vitamin B1 Quiz (USMLE)

Which of the following is the coenzyme form of Thiamine?

A) TPP (Thiamine pyrophosphate)

B) TMP (Thiamine mono phosphate)

C) TTP (Thiamine triphosphate)

D) Free thiamine

E) TAD (Thiamine adenine dinucleotide).

Cobalamin (Vitamin B 12) (Antipernicious Anemia)

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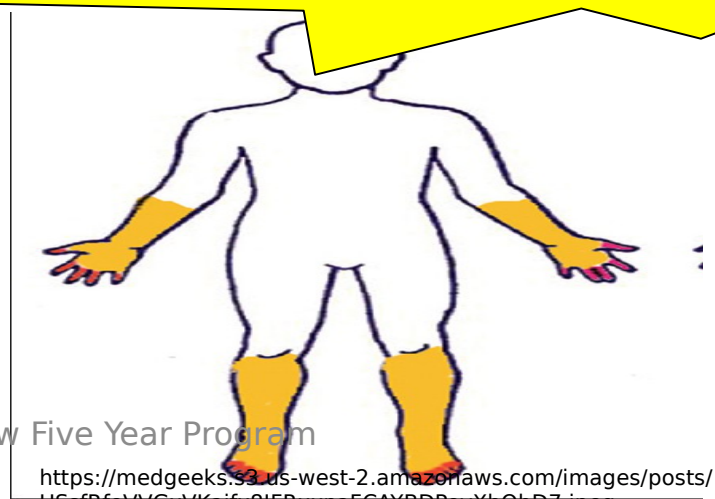
Case scenario

A 22-year-old man on a vegetarian diet presents to clinician with poor memory and tingling & numbness over hand and feet. Examination revealed decreases sensation hand and feet with paraesthesia .Laboratory investigation revealed megaloblastic anemia

What is the suspected diagnosis?



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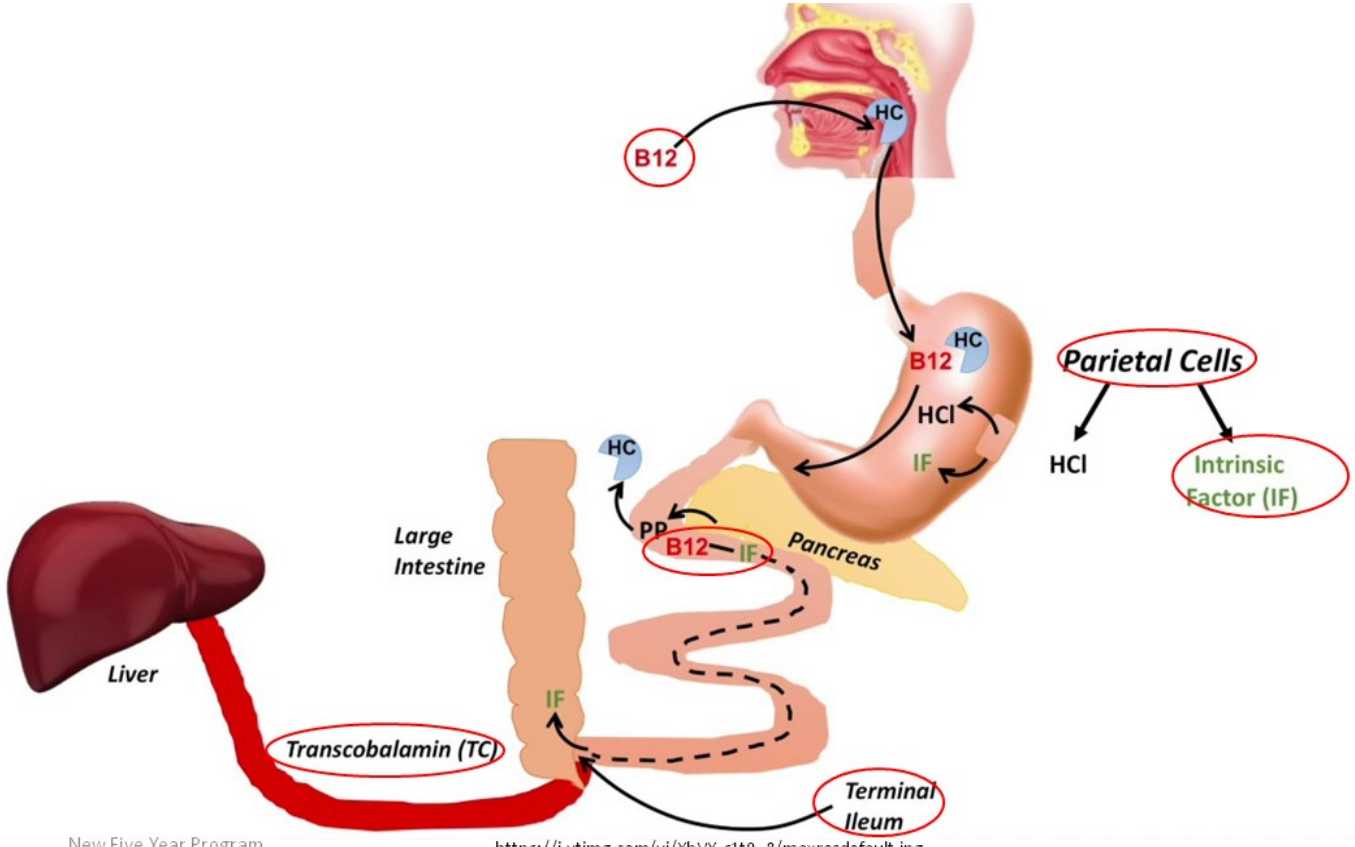
Cobalamin (Vitamin B 12) (Antipernicious Anemia

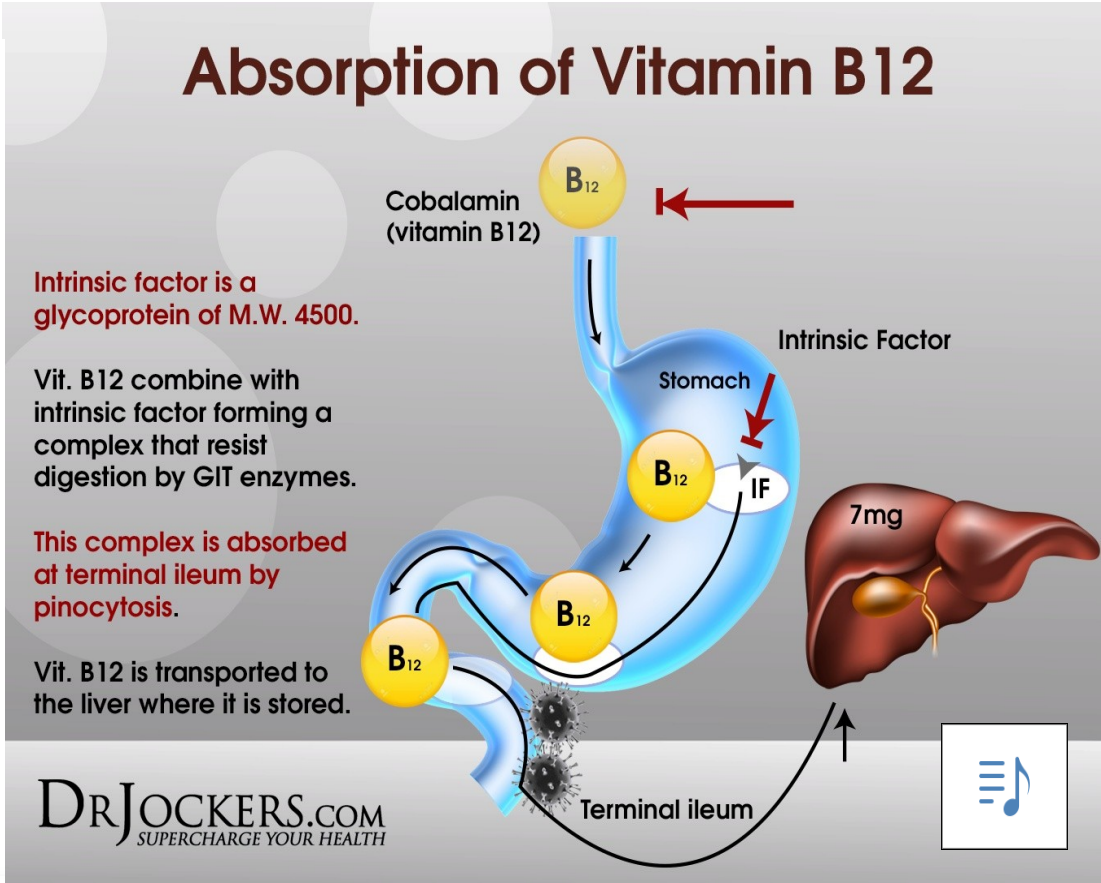
Sources: Animal only so deficient in vegetarians'.

Absorption:

- Vitamin B_{12} (***extrinsic factor***) + IF (***intrinsic factor***) from parietal cells forming ***IF–B_{12} complex***
- IF-B_{12} complex in the gut binds to specific receptors on the mucosal cells of the ileum.
- B_{12} is transported into the mucosal cells and then into portal circulation.
- Lack of IF prevents the absorption of vitamin B_{12}, resulting in pernicious anemia.

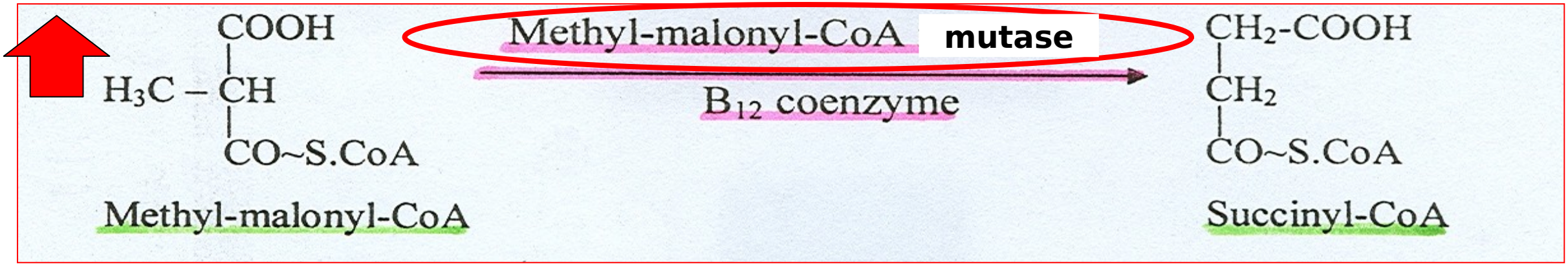
- **cobalamin are transported in plasma as *Transcobalamin II-vitamin B12 complex***
- **In the liver, cobalamin is stored attached to a protein *(transcobalamin I)*. Liver stores provide up to 1-5 years supply of B_{12}**

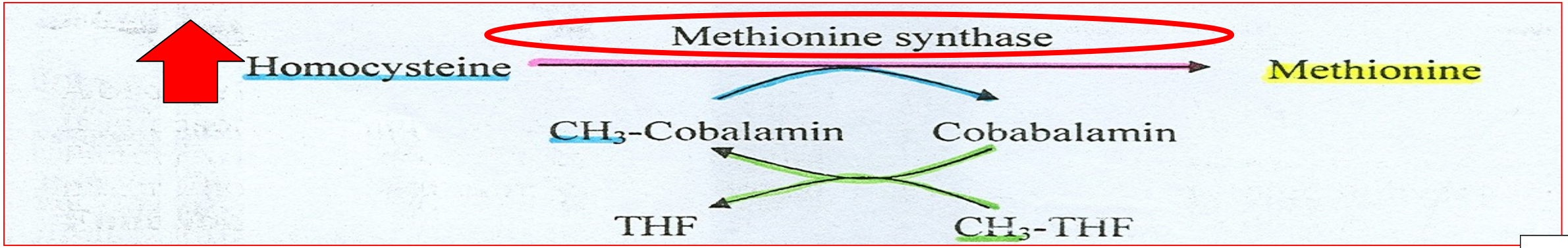




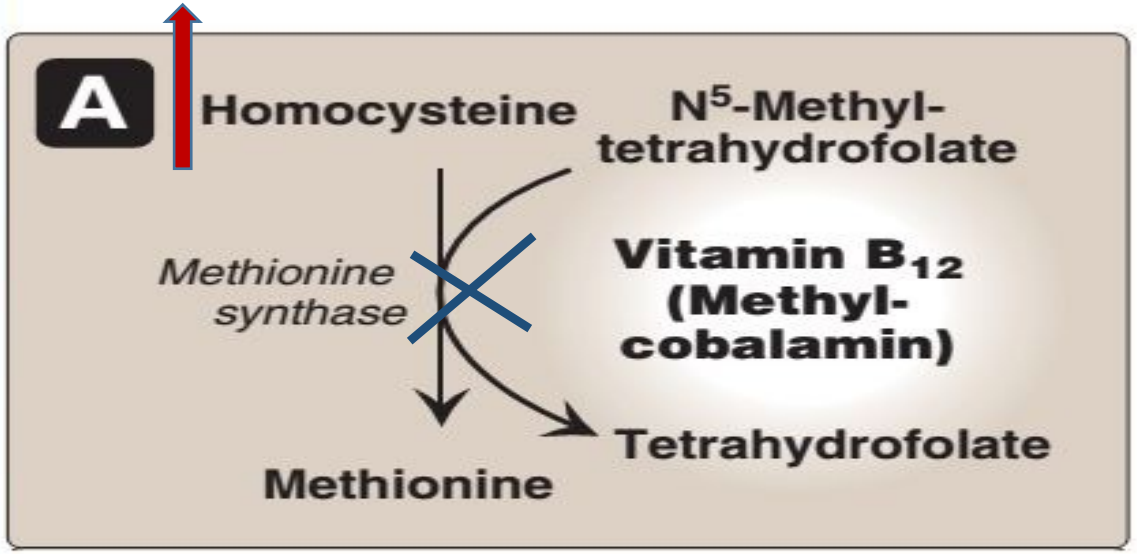
Function of Vitamin B12

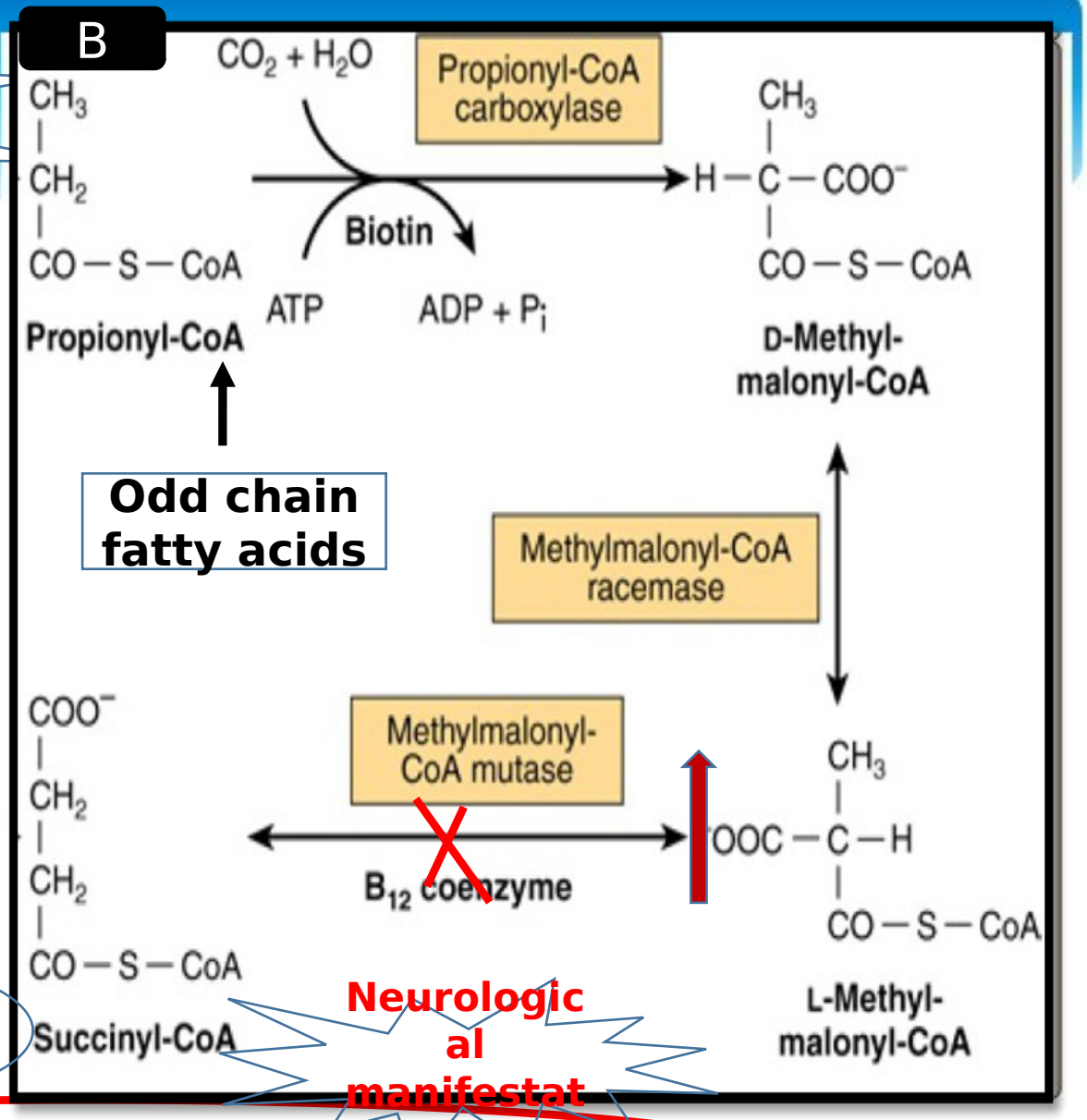
Acts as coenzyme for the following enzymes :





methylemalonyl COA aciduria found in urine in cases of vitamin B12 deficiency





In vitamin B12 deficiency

Neurological manifestations

Reactions requiring coenzyme forms of vitamin B12.

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Deficiency of Vitamin B12

Causes :

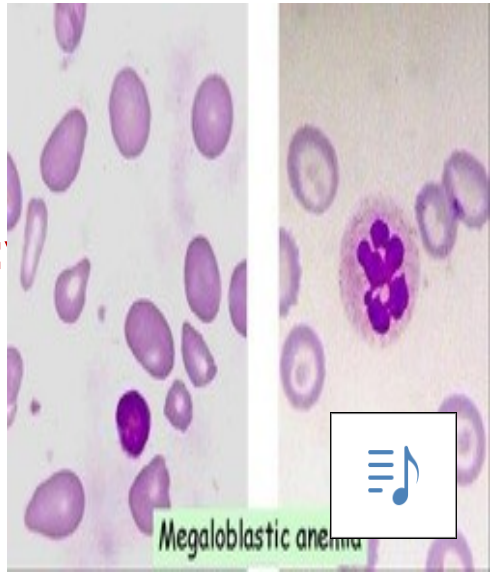
- **Failure of absorption of B_{12}**
  - **Malabsorption diseases**
  - **Gastrectomy or operation for obesity treatment(Bypass operation & gastric sleeve; bariatric surgery) or gastric or small intestine resections**
  - **Autoimmune destruction of the gastric parietal cells** (IF) → **pernicious anemia**
  - **Malfunctioning of gastric parietal cells e.g. in elderly subjects → decreased secretion of intrinsic factor→ B12 malabsorption.**
  - **Drugs as antacids as proton pump inhibitors which inhibit action of partial cells cause decreased secretion of both B12 & HCL.**
- **Dietary deficiency** among **vegetarians'**.

Manifestations :

A- Megaloblastic anemia or Leukopenia or thrombocytopenia or Panc

due to functional folate deficiency which results in accumulation of **methyl-THF** leading to **folate trap.**

Explain on a biochemical basis



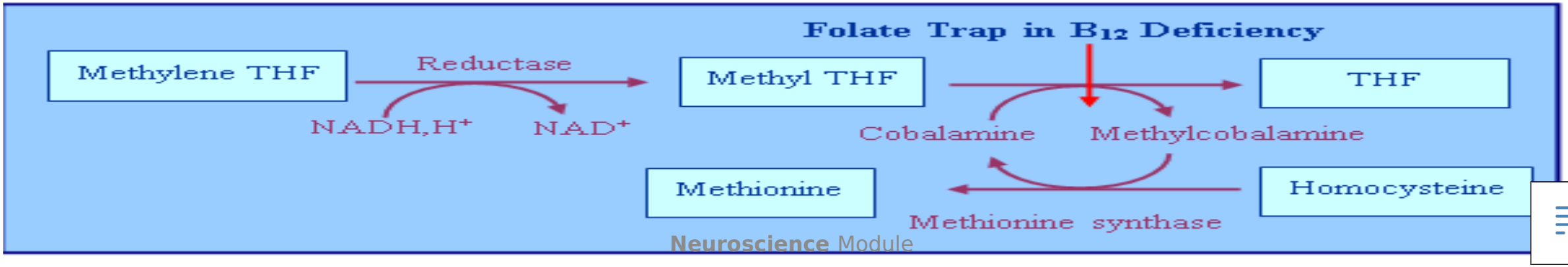
Folate trap (methyl folate trap)

The production of methyl THF is an irreversible step.

Therefore the only way to re-generate THF is mediated by cobalamine ***(B_{12})***.

In case of cobalamine (B_{12}) deficiency folate is trapped as methyl-THF.

So it is a functional deficiency of folic acid

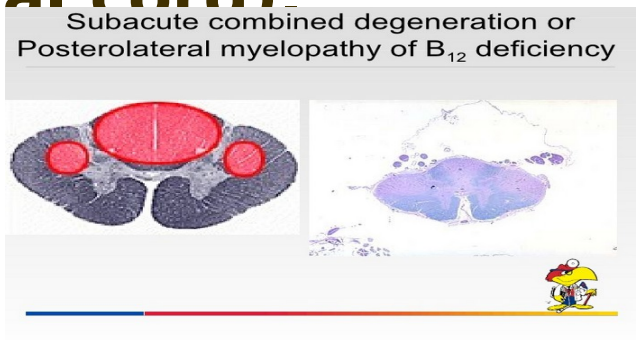


Deficiency of Vitamin B12

B- Neurological manifestations and methylmalonic aciduria :

- **Peripheral neuritis**
- **Sub acute combined degeneration of spinal cord (atrophy of the lateral and posterior columns of spinal cord)**

This is due to accumulation of methylmalonyl-CoA



1.acts as competitive for malonyl-CoA and produces inhibition of fatty acid biosynthesis required for synthesis of myelin sheath.

2- substitute malonyl-CoA in fatty acid synthesis leading to production of branched-chain fatty acids which disrupt membrane structure

Neurological manifestations of vitamin B12 deficiency

deficiency

1. Cerebrum:

- ✓ Complex neuropsychiatric symptoms: Delusion, illusion, hallucination, cognitive impairment, dementia, optic atrophy.

2. Spinal cord:

- ✓ Subacute combined degenration of spinal cord
- ✓ Post column: Diminished vibration sensation and proprioception.
- ✓ Corticospinal tract: Upper motor neuron sign.

3. Peripheral Nerve:

- ✓ Tingling & numbness.
- ✓ Glove and stocking paraesthesia.
- ✓ Loss of ankle reflex.

- Peripheral nerves are usually affected first, and patients complain initially of paresthesias.
- The posterior columns next become impaired, and patients complain of difficulty with balance.

https://image.slidesharecdn.com/vitb12def-161219175209/95/vit-b12-deficiency-causes-and-management-34-638.jpg?cb=1482169961

Deficiency of Vitamin B12

C-Hyperhomocysteinemia and thrombosis and hypertension:

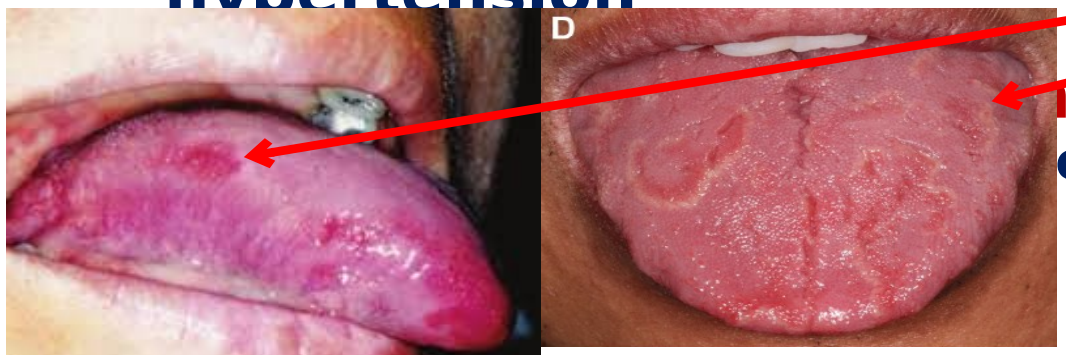
- **Elevated blood level of homocysteine is a significant risk factor for development of atherosclerosis and hypertension due to decrease of methionine:**

➢ **Methionine is sulfur containing amino acid enter in the**

➢ **Methionine is also needed for S-Adenosyl methionine (SAM) needed for methylation reactions during heparin synthesis.**

Explain on a biochemical basis

➢ **So the net result is defect in heparin structure & synthesis leads to defective functions of heparin thrombosis & hypertension**



Increased homocysteine blood level of in :

- **Vitamin B6 deficiency**
- **Vitamin B12 deficiency**
- **Folic acid deficiency**

Treatment of Vitamin B12 Deficiency

Vitamin B12 deficiency & anemia is usually treated with:

- **Intramuscular injections of vitamin B12, in a form (cyanocobalamin or hydroxocobalamin). At first, these injections every other day for two weeks, or until symptoms have stopped and improving then every month for 2-3 months.**
- **Vitamin B12 not given orally & must given as intramuscular injections in the patient taking antacids drugs (as proton pump inhibitors or H2 blocker) because :**

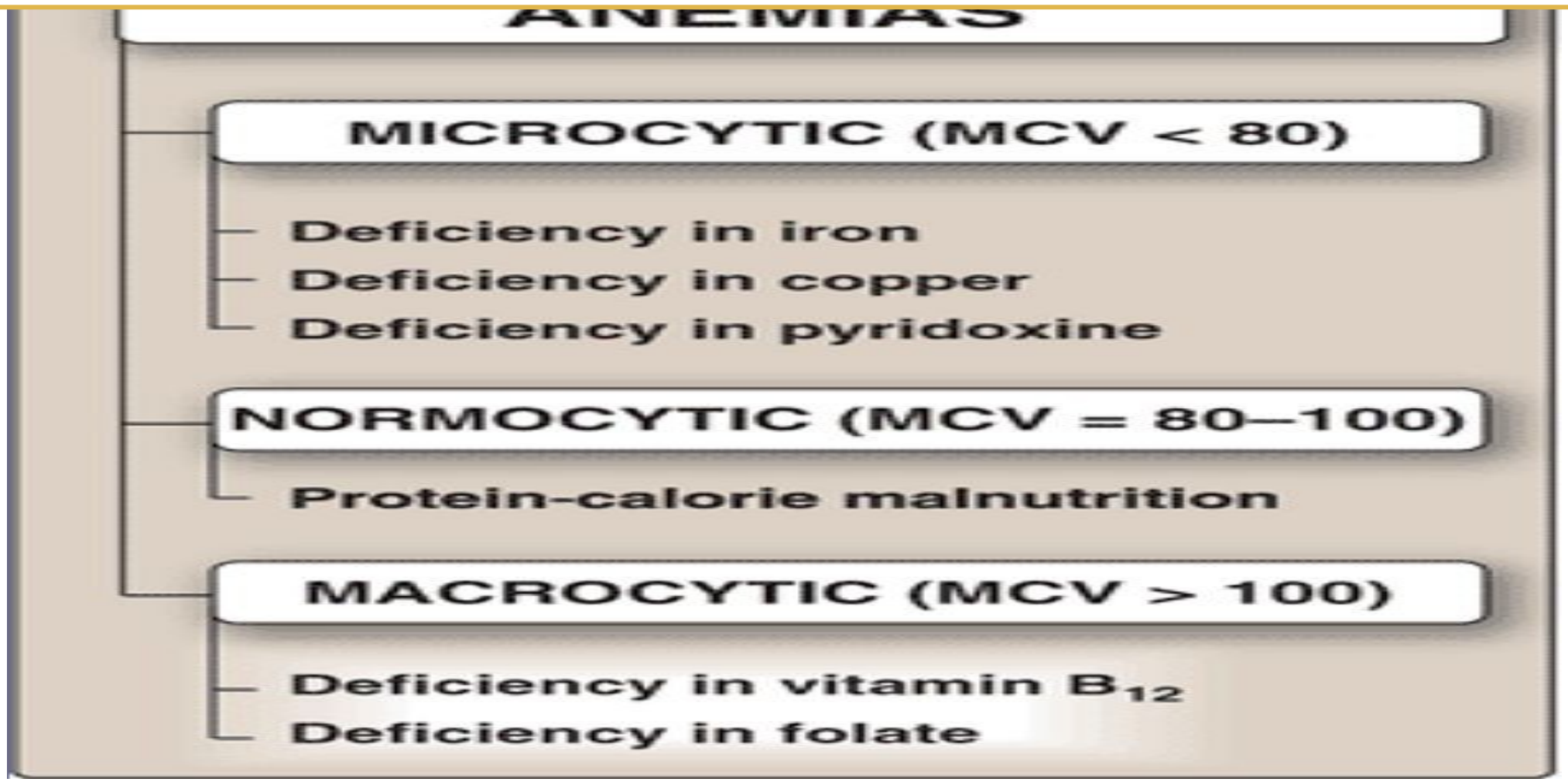
- Antacids will decease HCL secretion which is important for vitamin B12 absorption so it must be given as intramuscular injections

-Some antacids inhibit action of part **Explain on a biochemical basis** **of both B12 & HCL decreasing B12 absorp**

- **Also if vitamin B12 deficient in diet as vegetarian or vegan diet: patient should take diet rich in vitamin B12 or vitamin B12 tablet in absence of antacids or other factor affecting its absorption as pernicious anemia & bariatric surgery or gastric or small intestine resections**

Classification of nutritional anemia's by RBCs cell size

The normal mean corpuscular volume (MCV) for people older than age 18 is between 80 and 100 µ;m3.



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Vitamin B12 Deficiency Quiz (USMLE)

A 42-year- old woman presents to physician with frontal headache , painful tongue & tingling & numbness over hand and feet. Examination revealed decreases sensation hand and feet ,hypertension & beefy red patch in the tongue. Laboratory investigation revealed megaloblastic anemia .

Which one of the following vitamin deficiency is suspected?

A. Vitamin A

B. Vitamin B12

C. Vitamin B9

D. Vitamin B1

SUGGESTED TEXTBOOKS

- "Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R.Ferrier
- "Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W.Rodwell.
- Fundamentals of Clinical Chemistry (Tietz) Sixth
- "Textbook of Biochemistry with Clinical Correlations" by T.M.Devlin
- ***www.namrata.co- Biochemistry for medics***

Lecture Summary

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2. Functions of B1 & 12 vitamins
3. Vitamins (B1& B12) deficiencies & their clinical disorders

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